

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY  
DEPARTMENT OF PESTICIDE REGULATION  
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

FONOFOS

Chemical Code # 000254, Tolerance # 00221  
SB 950 # 149

August 20, 1997

Revised: 3/31/98

I. DATA GAP STATUS

Combined, rat:	No data gap, no adverse effect.
Chronic toxicity, dog:	No data gap, no adverse effect.
Oncogenicity, mouse:	No data gap, no adverse effect.
Reproduction, rat:	Data gap, inadequate study, no adverse effect indicated.
Teratology, mouse:	No data gap, possible adverse effect.
Teratology, rabbit:	No data gap, possible adverse effect.
Gene mutation:	No data gap, no adverse effect.
Chromosome effects:	No data gap, possible adverse effect.
DNA damage:	No data gap, no adverse effect.
Neurotoxicity:	No data gap, possible adverse effect <sup>1</sup> .

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Toxicology one-liners are attached.

1 - A study is on file for the neurotoxicity in hen. The acute and subchronic neurotoxicity studies in rat are acceptable with a possible adverse effect (not delayed neurotoxicity).

All record numbers through 159730 were examined.

\*\* indicates an acceptable study.

**Bold face** indicates a possible adverse effect.

File name: T980331

Toxicology summary by Green, Kishiyama & Silva, 8/20/97; Silva, 3/31/98

These pages contain summaries only. Individual worksheets may contain additional effects.

## II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

## COMBINED, RAT

\*\* 034 068624, "Rat Chronic Toxicity and Oncogenicity Study with Dyfonate," (Pavkov, K.L. and Taylor, D.O.N, ICI Americas Inc., Environmental Health Center, Farmington, CT., Report T-11997, 5/2/88). Dyfonate Technical (94% pure) was fed in diet to Sprague-Dawley (CD) rats (20 or 60/sex/dose) for 24 months at 0 (Purina Certified Rodent Chow # 5002), 3.7, 14.2, 57.7 or 116 ppm (sacrifice at 1 year). Chronic NOEL = 14.2 ppm (There was an increased incidence in loose stools and hair loss, primarily in females at 57.7 ppm. There was a significant decrease in female body weights at 116 ppm. There was an increase in ophthalmological effects in females at 116 ppm. Female relative (%brain) adrenal, kidney and liver weights were decreased at 116 ppm.) Oncogenicity NOEL  $\geq$  57.7 ppm. ChE NOEL = 14.2 ppm (The RBC, serum and brain ChE were significantly inhibited at  $\geq$  57.7 ppm.) **Acceptable**. (H. Green & M. Silva, 7/11/97).

## CHRONIC TOXICITY, RAT

023 041994, "Dyfonate (N-2790), Safety Evaluation by Dietary Administration to Rats for 105 Weeks", (Woodard, G., Woodard Research Corporation, Herndon, VA., 10/1/68). Dyfonate Technical (99.5%-99.9% pure) was fed in the diet to albino rats (30/sex/dose) for 105 weeks at 0 (basal ration), 10.0, 31.6, and 100 ppm. Chronic NOEL = 31.6 ppm (Clinical symptoms: nervous behavior and tremors were observed, primarily in females at 100 ppm.) ChE NOEL = 10 ppm (Plasma and RBC cholinesterase were reduced 57%-85% at  $\geq$  31.6 ppm in both sexes. Brain ChE was decreased at 100 ppm in both sexes). **Unacceptable**, not upgradeable (inadequate hematology, serum chemistry, histopathology, urinalysis, ophthalmology). (Green & Silva, 7/14/97)

018 935744, Incomplete version of 041994.

## CHRONIC TOXICITY, DOG

**023 041993**, "Dyfonate (N-2790), Safety Evaluation by Dietary Administration to Dogs for 106 Weeks", (Woodard, G., Woodard Research Corporation, Herndon, VA., 1/9/69). Dyfonate (N-2790) Technical (99.5%-99.9% pure) was fed in the diet to Beagle dogs (4/sex/dose) for 106 weeks at 0 (Dietrich and Gambrell dog meal), 16 (reduced to 8.0 ppm at week 14), 60, and 240 ppm. Chronic NOEL < 8 ppm (There were muscle fasciculations at 8 ppm. At 240 ppm, liver weights were increased (primarily in males) and prostate weights were decreased. At 240 ppm, there was increased mortality and clinical symptoms and decreased food consumption and body weight gain. There was, at 240 ppm, an increase in basophilic granulation of muscularis in the small intestine and increased binucleated hepatic cell pigmentation and eosinophilia in hepatocellular cytoplasm.) ChE NOEL = 8 ppm (There was inhibition of plasma and erythrocyte ChE at  $\geq$  60 ppm.) **Possible adverse effect**. There was significant inhibition of RBC and plasma ChE. There was increased mortality and CNS effects. **Unacceptable**, possibly upgradeable (A NOEL was not achieved in this study. Dose level justification, dosing material analyses, clinical symptoms incidence data and statistical analyses of results are requested.). (Green & Silva, 7/17/97).

017 935743, Incomplete version of 041993.

\*\* 064 143513 "Fonofos: 1 Year Oral Toxicity Study in Dogs," (Hodge, M.C.E., Zeneca Central Toxicology Laboratory, Cheshire, UK; Report No. CTL/P/4499; Study No. PD0944;12/14/95). Fonofos (purity = 94.6%) was administered via gelatin capsules to Beagle dogs (4/sex/dose) at 0 (corn oil), 0.2, 1.0 or 1.75 mg/kg/day to 4 beagle dogs/sex/group for 1 year. Half the number of high dose dogs were dosed at 2 mg/kg on the first 2 days of dosing, then dosing was suspended 2 days (death of 1 high dose female) and then resumed, but at 1.75 mg/kg/day. Chronic NOEL = 1.0 mg/kg/day (Clinical signs were increased in both sexes at 1.75 mg/kg/day. Albumin, total protein, alkaline phosphatase and calcium levels were affected by fonofos treatment. Liver weights were increased at 1.75 mg/kg/day. ChE NOEL = 0.2 mg/kg/day (RBC and plasma ChE were significantly inhibited in both sexes at  $\geq 1.0$  mg/kg/day.) **No adverse effect.** ACCEPTABLE. (Kishiyama & Silva, 7/18/97).

#### ONCOGENICITY, RAT

See Combined, Rat.

#### ONCOGENICITY, MOUSE

\*\* 032 068459, "Final Report, 18-Month Dietary Oncogenicity Study with Dyfonate Technical in Mice", (Sprague, G.L. & Zwicker, G.M., Stauffer Chemical Co., Environmental Health Center, Farmington, CT., Report # T-11995, 3/12/87). Dyfonate Technical (94.0% pure) was fed in the diet to CD-1 (CrI:CD-1[ICR]-BR[Swiss]) mice (60/sex/dose) at 0 (Purina Certified Rodent Chow # 5002), 4.6, 23.5, and 94.7 ppm for 18 months. Chronic NOEL = 23.5 ppm (Bodyweights and food consumption were significantly decreased at 94.7 ppm. There was an increased incidence in duodenal hyperplasia and hypertrophy in both sexes, primarily at 18 months, at 94.7 ppm.) ChE NOEL = 23.5 ppm (There was a significant decrease in serum, rbc and brain ChE at 94.7 ppm.). Oncogenicity NOEL  $\geq 94.7$  ppm. **No adverse effect. Acceptable.** (Green & Silva, 7/16/97).

#### REPRODUCTION, RAT

024 041995, "Dyfonate (N-2790), Three-Generation Reproduction Study in Rats," (Woodard, G., Woodard Research Corporation, Herndon, VA., 1/10/69). Dyfonate (N-2790,  $\geq 99.8\%$  pure) was fed in the diet for 3 generations (2 litters per generation) to albino (CD - random bred Sprague-Dawley descendants) rats (17-23/sex/dose) at nominal concentrations of 0 (Purina Laboratory Chow meal supplemented with one per cent U.S.P. cod liver oil), 10.0, and 31.6 ppm. Parental NOEL  $\geq 31.6$  ppm (nominal). Reproductive NOEL  $\geq 31.6$  ppm (nominal). The doses in the study were not sufficiently high to test for possible adverse effects. **Unacceptable**, not upgradeable (histopathology on parental animals, sacrifice of F1a pups at birth, dosing material analyses, dose level justification). (Green & Silva, 7/23/97).

017 935746, Incomplete version of 041995.

#### TERATOLOGY, RAT

No study on file at this time.

## TERATOLOGY, MOUSE

**\*\* 024, 047 041998, 093397**, "A Teratology Study in CD-1 Mice with Dyfonate\* Technical," (Minor, J.L., Stauffer Chemical Co., Environmental Health Center, Farmington, CT., Report # T-10192, 4/2/82). Dyfonate Technical (95.6% pure) was administered to mated female CD-1 mice (29-30/sex/dose) by gavage on gestation days 6 through 15 at 0 (corn oil), 2, 4, 6, and 8 mg/kg/day. **Maternal NOEL** = 4 mg/kg/day (Body weight, body weight gain and food consumption were significantly decreased at 8 mg/kg/day. Two treatment-related deaths occurred at 6 mg/kg/day. The maternal incidence of dacryorrhea, chromodacryorrhea, and tremors was increased at 8 mg/kg/day.) **Developmental NOEL** = 2 mg/kg/day (There was an increase in the incidence of dilated 4th brain ventricle and other soft tissue anomalies at  $\geq 4$  mg/kg/day. There was also a significant increase in sternebral developmental effects at 8 mg/kg/day.). **Possible adverse effect. Acceptable.** (Green & Silva, 7/29/97).

017 935745, Incomplete version of 041998.

## TERATOLOGY, RABBIT

**\*\* 033 068623**, "A Teratology Study in Rabbits with Dyfonate Technical, T-12630, Volume 1: Final Report," (Sauerhoff, M.W., WIL Research Laboratories, Inc., Ashland, OH., Study # WIL-27027, 2/23/87). Dyfonate Technical (94% pure) was administered by gavage to 18 artificially inseminated female New Zealand White rabbits per dose on gestation days 7 through 19 at 0 (corn oil), 0.2, 0.5, and 1.5 mg/kg/day. **Maternal NOEL** = 0.5 mg/kg/day (There was an increase in post-implantation loss and a decrease in urination and defecation, primarily at 1.5 mg/kg/day.) **Developmental NOEL** > 1.5 mg/kg/day (There were no effects at any dose.) **Possible adverse effect:** increased post-implantation loss. **Acceptable.** (Green & Silva, 8/1/97)

## GENE MUTATION

**\*\* 031 068264**, "Mutagenicity Evaluation in *Salmonella Typhimurium*, Final Report", (Majeska, J.B.; Stauffer Chemical Co., Environmental Health Center, Farmington, CT., Report # T-12841, 5/20/86). Dyfonate (94% pure) was used in a reversion assay in triplicate with plates *Salmonella Typhimurium* strains TA1535, TA1537, TA100, and TA98 (+/- metabolic activation) at untreated, 0 (DMSO), 0.0125, 0.0250, 0.0500, 0.1000, and 0.2000  $\mu$ l/plate. **No increase in revertants. Acceptable.** (Green & Silva, 8/14/97).

031 068265, "Mutagenicity Evaluation in L5178Y Mouse Lymphoma Multiple Endpoint Test Forward Mutation Assay, Final Report", (Hertzel, K.M., Majeska, J.B., Stauffer Chemical Co., Environmental Health Center, Farmington, CT., Report # T-12796, 4/30/86). Dyfonate (94% pure) was used in a forward mutation assay in duplicate with L5178Y (TK+/-) mouse lymphoma cells (+/- S-9 from male Sprague-Dawley rats induced with Aroclor 1254) at untreated, 0 (DMSO), 0.0025, 0.0050, 0.0100, 0.0200, 0.0300, or 0.0400  $\mu$ l/ml. **No increase in forward mutations. Not acceptable** (No repeat trial.) **Not upgradeable.** (Green & Silva, 8/18/97)

017 027748, "In Vitro Microbiological Mutagenicity and Unscheduled DNA Synthesis Studies of Eighteen Pesticides", (SRI International, Project LSU-3493, August 1978), Fonofos, 96.9% purity, reversion assay using *Salmonella Typhimurium* strains TA1535, TA1537, TA1538, TA100, and TA98 with and without activation (Aroclor 1254 (500 mg/kg) induced male Sprague-Dawley rat liver fraction) at 0 (DMSO), 1, 10, 50, 100, 500, 1000, or 5000  $\mu$ g/plate. **No increase in reversion rate** is reported. **Unacceptable**, not upgradeable (single plates, no confirming assay for high dose). (A. Apostolou, 5/224/85)

017 027749, "In Vitro Microbiological Mutagenicity and Unscheduled DNA Synthesis Studies of Eighteen Pesticides", (SRI International, Project LSU-3493, August 1978), Fonofos, 96.9% purity, reversion assay using *Escherichia coli* strain WP2 (uvrA) with and without activation (not specified) at 0, 1, 10, 50, 100, 500, 1000, or 5000 µg/plate. **No increase in reversion rate** is reported. **Unacceptable**, not upgradeable (single plates, no confirming assay for high dose). (A. Apostolou, 5/24/85)

024 041996, Duplicate of 027748 and 022749.

\*\*043 095889, "Fonofos - An Evaluation of Mutagenic Potential Using *S. Typhimurium*", (R. D. Callander, ICI Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK., Report # CTL/P/3153, 21 December 1990). Fonofos (94.9% w/w pure) was used on *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 (exposed for 3 days) in the presence and absence of metabolic activation (2x positive controls; 3x test material or 4x negative controls) at 0 (DMSO), 0.32, 1.6, 8.0, 40.0, 200.0, 1000.0, or 5000.0 µg/ml. There was no indication of increased mutagenesis due to exposure to fonofos. The positive controls functioned as expected. **Acceptable**. (Green & Silva, 8/18/97)

### CHROMOSOME EFFECTS

\*\*045 089359, "Fonofos: An Evaluation in the In Vitro Cytogenetic Assay in Human Lymphocytes", (N. James and J. M. Mackay, ICI Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK., Report # CTL/P/3263, 13 March 1991). Fonofos technical (94.9% w/w pure) was used on human peripheral blood lymphocytes (1 donor/sex) in duplicate (+/- S9 activation) for 3 hours at 0 (DMSO), 10, 50, and 100 µg/ml. Chromosomal damage is not indicated. **Acceptable**. (Green & Silva, 8/19/97).

\*\* 044 092051, "Fonofos: An Evaluation in the Mouse Micronucleus Test", (K. Jones and J. M. Mackay, ICI Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK., Report # CTL/P/2827, 17 January 1990). Fonofos technical material (100% w/w pure) was used. C57BL/6JfCD-1/Alpk (15 mice/sex/dose) received a single dose by gavage at 0 (corn oil), 6.0, and 9.5 mg/kg. Bone marrow from 5 per sex per group was sampled at 24, 48, and 72 hours. **Increased frequency of micronucleated polychromatic erythrocytes was not observed.** **Acceptable** (Green & Silva, 8/19/97).

### DNA DAMAGE

\*\* 031 068458, "Mutagenicity Evaluation in L5178Y Mouse Lymphoma Multiple Endpoint Test Cytogenetic Assay, Final Report", (O'Lone, S.D., Snyder, R.D., Stauffer Chemical Co., Environmental Health Center, Farmington, CT., Report # T-12797, 5/20/86). Dyfonate\* (94% pure) was used in a cytogenetic assay for chromosomal aberrations (4 hour exposure, duplicate cultures, +/- S9) at untreated, 0 (DMSO), 0.0050, 0.0100, 0.0150, 0.0200, 0.0250, 0.0300 or 0.0400 µl/ml. **Increased structural (with activation) and numerical (non-activated) chromosomal aberrations.** **Acceptable**. (Green & Silva, 8/18/97)

017 027747, "In Vitro Microbiological Mutagenicity and Unscheduled DNA Synthesis Studies of Eighteen Pesticides", (SRI International, Project LSU-3493, August 1978), Fonofos, 96.9% purity, mitotic recombination assay using *Saccharomyces cerevisiae* D3 with and without activation (not specified) at 0 (DMSO), 0.1, 0.5, 1.0, 2.0, 4.0, or 5.0 w/v or v/v with 3 or 5 plates per level. **No increase in mitotic gene conversion** is reported. **Unacceptable**, not upgradeable (insufficient number of plates, DMSO as vehicle). (A. Apostolou, 5/24/85)

017 027750, "In Vitro Microbiological Mutagenicity and Unscheduled DNA Synthesis Studies of Eighteen Pesticides", (SRI International, Project LSU-3493, August 1978), Fonofos, 96.9% purity, unscheduled DNA synthesis assay using WI-38 cells with and without activation (liver homogenate from adult Swiss-Webster mice) at 0 (DMSO), 0.1, 1.0, 10.0, 100, and 1000 µg/ml with 6 replicates per dose level. Test article precipitation reportedly occurred at 100 and 1000 mg/ml. **No increase in unscheduled DNA synthesis** is indicated. **Unacceptable**, may be upgradeable (historical controls). (A. Apostolou, 5/24/85)

024 041997, Duplicate of 027749 and 027750.

## NEUROTOXICITY

**\*\*051 128132**, "Fonofos, Acute Delayed Neurotoxicity Study in Domestic Hen" (V. A. Redgrave, Huntingdon Research Centre Ltd., P.O. Box 2, Huntingdon, Cambridgeshire, PE18 6ES, England, Report # ISN 316/931844, 11/8/93). Fonofos (Dyfonate technical, 94.2% pure) was administered in a single dose by gavage to hybrid brown laying hens (12 or 34/dose) at 0 or 143 mg/kg with protection (20 mg/kg atropine sulphate), followed by a 21/22 day observation. Delayed Neurotoxicity NOEL = 143 mg/kg. NOAEL = 0 mg/kg (Signs of toxicity at 143 mg/kg included mortality, unsteadiness, inability to stand, and subdued behavior, survivors recovered by day 6 post-dosing. Histopathology revealed five of six negative control birds with trace axonal degeneration in at least one level of spinal cord and/or peripheral nerve. Trace axonal degeneration in at least two levels of spinal cord and one level of peripheral nerve was seen in all six 143 mg/kg birds, along with trace axonal degeneration in the cerebellum in one bird. One 143 mg/kg hen was noted with significant axonal degeneration (moderate or marked).) ChE NOEL < 143 mg/kg (Brain AChE levels at 143 mg/kg were reduced 51% compared to negative controls.) **Possible adverse effect: Axonal degeneration of the tibial nerve was observed.** **Acceptable.** (Green & Silva, 8/1/97).

025 041999, "Neurotoxicity of 90-Day Oral Administration of Technical Dyfonate (T-6237) to Adult Hens (Revised)", (Miller, J.L., Stauffer Chemical Co., Richmond Toxicology Laboratory, Richmond, CA., 11/8/78). Technical Dyfonate (93.5% pure) was administered by gavage White Leghorn hens (10/dose) for 90 days at untreated, 0 (corn oil), 2, 4, and 8 mg/kg/day. NOEL < 2 mg/kg/day (Clinical symptoms were increased and egg laying was decreased at all doses. Body weights were significantly decreased at  $\geq 4$  mg/kg/day.) ChE NOEL < 2 mg/kg/day (Cholinesterase was significantly decreased at all doses.) **No increase in delayed neuropathy** is reported. **Unacceptable**, upgradeable (dosing material analyses). (Green & Silva, 8/4/97).

017 935742, Incomplete version of 041999.

**025 042000**, "N-2790 (Dyfonate), Demyelination Study in Chickens", (Woodard, M.W. and Woodard, G.; Woodard Research Corporation, Herndon, VA., 9/23/66). N-2790 Technical (99.8% pure) was fed in the diet to White Leghorn hens (10/dose) for 46 days at 0 (Purina Cage Layena), 2.0, 6.32, or 20.0 mg/kg/day. NOEL = 6.32 mg/kg/day (Increased clinical symptoms and decreased bodyweight and food intake were observed at 20.0 mg/kg/day.) **Possible adverse effect: demyelination of the peripheral nerve** at 20 mg/kg/day was observed. **Supplemental** information. (Green & Silva, 8/5/97).

017 935757, Incomplete version of 042000.

**\*\* 048, 065 122695, 159728** "Fonofos: Acute Neurotoxicity Study in Rats", (J.M. Horner, ZENECA Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK., Report #: CTL/P/3946, 3/17/93). "First Supplement to Fonofos: Acute Neurotoxicity Study in Rats," (Horner, J.M.; Report #: CTL/P/3946; Study #: AR5434; Zeneca CTL, Cheshire, UK; 12/6/95). Fonofos technical (94.6% pure) was administered in a single dose by gavage to Alpk:APfSD rats

(10/sex/dose) at 0 (corn oil), 2, 4, and 7 mg/kg. Treatment was followed by a 14 day observation, with a functional observational battery performed at pre-treatment and on days 1 (6-7 hours after dosing), 8, and 15. Systemic NOEL = 4 mg/kg (One female exhibited shaking and urinary incontinence after dosing and the incidence and the duration of diarrhea was increased in males at 7 mg/kg.). Neurotoxicity NOEL = 7 mg/kg. No adverse effect. **Previously reviewed as unacceptable** (Test article certificate of analysis requested. No positive controls and inadequate presentation of clinical signs. Silva, 8/11/97) Upon submission of the requested information, the study has been upgraded to acceptable. M. Silva, 3/26/98.

**\*\* 049, 066 124151, 159730** "Fonofos: Subchronic Neurotoxicity Study in Rats", (J. M. Horner, Zeneca Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK., Report # CTL/P/3879, 4/27/93). "First Supplement to Fonofos: Subchronic Neurotoxicity Study in Rats," (J. M. Horner, Zeneca Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK., Report # CTL/P/3879, 11/21/95). The test article is identified as fonofos unformulated technical material with 94.6% w/w purity. 12 Alpk:APfSD rat per sex per group received 0 (CT1 diet), 15, 50, or 125/150 (level was increased from 125 to 150 from week 5) ppm w/w for 13 weeks. Clinical NOEL = 50 ppm (There were increased clinical effects, and decreased brain weight at 125/150 ppm.) Cholinesterase NOAEL = 50 ppm (Brain, plasma and RBC ChE were significantly decreased at  $\geq 15$  ppm in both sexes.) Neurotoxicity NOEL = 50 ppm (Sciatic nerve fiber degeneration for 125/150 ppm males was observed. Landing foot splay, tail-flick response and grip strength were affected at 125/150 ppm.) **Possible adverse effect. Previously reviewed as unacceptable** (Test article clarification is requested. No positive control data. Silva, 8/12/97). Upon submission of the requested information, the study is upgraded to acceptable. Silva, 3/26/98.